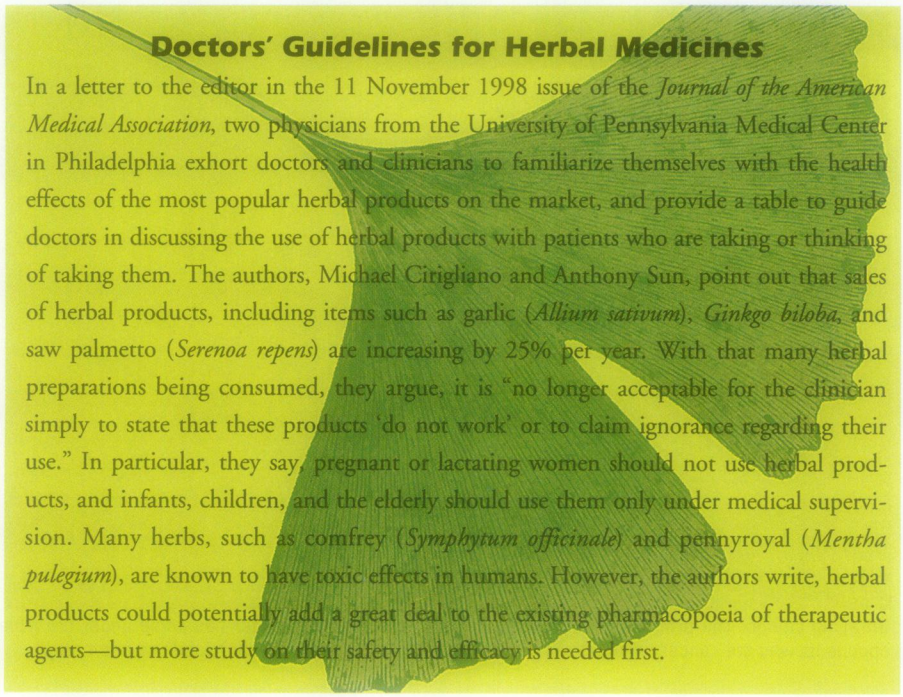

Doctors' Guidelines for Herbal Medicines

In a letter to the editor in the 11 November 1998 issue of the *Journal of the American Medical Association*, two physicians from the University of Pennsylvania Medical Center in Philadelphia exhort doctors and clinicians to familiarize themselves with the health effects of the most popular herbal products on the market, and provide a table to guide doctors in discussing the use of herbal products with patients who are taking or thinking of taking them. The authors, Michael Cirigliano and Anthony Sun, point out that sales of herbal products, including items such as garlic (*Allium sativum*), *Ginkgo biloba*, and saw palmetto (*Serenoa repens*) are increasing by 25% per year. With that many herbal preparations being consumed, they argue, it is "no longer acceptable for the clinician simply to state that these products 'do not work' or to claim ignorance regarding their use." In particular, they say, pregnant or lactating women should not use herbal products, and infants, children, and the elderly should use them only under medical supervision. Many herbs, such as comfrey (*Symphytum officinale*) and pennyroyal (*Mentha pulegium*), are known to have toxic effects in humans. However, the authors write, herbal products could potentially add a great deal to the existing pharmacopoeia of therapeutic agents—but more study on their safety and efficacy is needed first.

specific antigen (PSA), an indicator of prostate cancer, had plummeted. The patient admitted he was taking PC-SPES, an herbal remedy derived from nine separate herbs and mushrooms that is sold over the Internet. DiPaola soon began to notice similar effects in other patients taking PC-SPES. He presented the case to Michael Gallo, the institute's associate director for basic science, who recalls: "I said, 'We've got an estrogen here. Let's take a look at these herbs.'"

DiPaola and Gallo turned their attention toward the men, conducting a clinical trial involving eight cancer patients taking the herbal remedy. They found that PC-SPES causes a decrease in testosterone and PSA, along with other symptoms of estrogen use. The researchers then enlisted George Lambert, a clinical pharmacologist at the NIEHS Environmental and Occupational Health Sciences Institute in Piscataway, New Jersey, to examine PC-SPES for estrogenic activity.

A yeast-based assay used by Lambert confirmed Gallo and DiPaola's suspicions that PC-SPES acts as an estrogen. "This is as potent as a drug," says DiPaolo. Says Gallo, "It was the collaboration of the expertise of these two centers that allowed us to make this discovery. This is the type of bioassay that should be done on herbal products." The three researchers and nine other colleagues reported their findings in the 17 September 1998 issue of the *New England Journal of Medicine* (*NEJM*).

Journal editors Marcia Angell and Jerome Kassirer used the report as a springboard for their editorial calling on the Food and Drug Administration (FDA) to require the same rigorous testing of alternative medicines that it requires of conventional drugs. PC-SPES, like other plant-derived substances, vitamins, minerals, and amino acids, is considered a dietary supplement. The FDA regulates supplement labeling but requires no testing.

The *NEJM* report hit a nerve among those who view herbal remedies as distinctly different—and safer—than their synthetic cousins. "I believed there was a possibility of a potential cure with this," says Mario Menelly, a PC-SPES user and subject in DiPaola's clinical trial. "It's nothing but herbs. It shouldn't hurt me." The article prompted a spate of letters to the editor from both sides of the issue, scheduled to be published in a future issue of *NEJM*.

In the long run, PC-SPES may be no more harmful than conventional treatment, but nobody knows for sure. Even proponents of herbal remedies recommend more clinical trials. "We need large-scale studies," says Sophie Chen, a professor of medicine at New York Medical College in Valhalla, who developed PC-SPES five years ago. "I would like to see it become a prescription medicine."

The yeast assay used to screen PC-SPES is among several developed in recent years that can measure estrogenic activity quickly and inexpensively. For a half-century, the only assay for estrogen required mice. Scientists fed mice the substance under study for several days, then sacrificed them and weighed their uteruses. Estrogenic substances cause the uterus to enlarge.

Mice assays are still considered the gold standard—DiPaolo and Gallo followed the yeast screening with a mouse assay—but may soon be replaced with yeast and other cellular assays. "It's less expensive," explains Elizabeth Jeffery, an associate professor of nutritional toxicology at the University of Illinois at Urbana–Champaign. "It's less labor-intensive. It's much more rapid." The yeast assay initially was used to screen PC-SPES for estrogen that binds to alpha receptors, which are found primarily in reproductive tissue. A few years ago, researchers discovered a second receptor, beta, that binds to estrogen in the brain, bone, kidneys, and other organs. Lambert's group is now developing a greater array of hormone receptor assays to screen the herbal remedy with beta receptors.

The yeast assay was constructed to simulate response of the human estrogen receptor system when exposed to an estrogenic mixture. When an estrogenic substance is added to the medium, the yeast proliferate. If the substance is not estrogenic, the yeast die. Like other screening assays, the yeast assay has limitations. It will not indicate activity in compounds that become estrogenic only after they're oxidized in the body, such as the pesticide methoxychlor. Differences in the permeability of yeast and human cell membranes also could confound results. "Something may not be able to get through the cell wall of yeast even though it gets through the cell membrane of humans," Lambert says.

To some cancer patients, like Mario Menelly, yeast assays and clinical trials don't mean a thing. Menelly is sticking with an unregulated mixture of herbs, even if it causes the same side effects as conventional, hormonal drugs. "It's only herbs," he says. "It comes from the earth."

His attitude is common. More than half of U.S. adults use dietary supplements, according to the FDA. Estimates of alternative-therapy usage among cancer patients range from 5% to 60%. "This isn't just a fad that'll go away in two months," says John Cardellina, director of botanical science for the Council for Responsible Nutrition, a trade organization representing manufacturers of dietary supplements. Cardellina laments the lack of information about dietary supplements for both consumers and physicians. "Doctors do not know enough about botanical products," he says. "They don't know what to expect in terms of efficacy and side effects. This [*NEJM* report] may get oncologists to look at PC-SPES and what it can do."